Microglia inhibit astrocyte-mediated neurodegeneration

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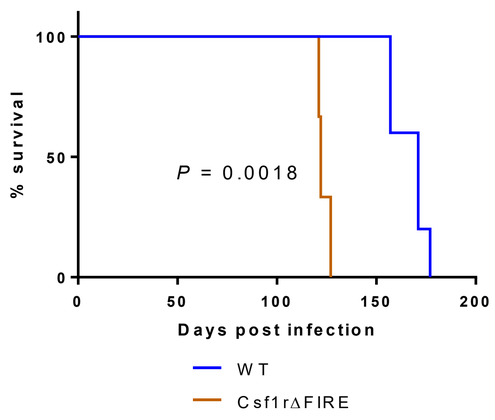
Introduction

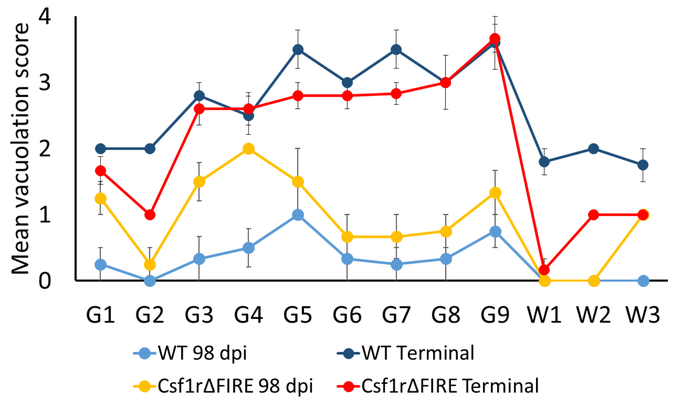
Prion diseases are infectious protein-misfolding disorders associated with neurodegeneration and glial activation in the CNS. Microglia have been suggested to play a critical role during prion disease. Mice deficient in microglia Csf1rΔFIRE develop normally. We challenged these mice with infectious prions in order to understand the role of microglia during neurodegeneration.

Methods

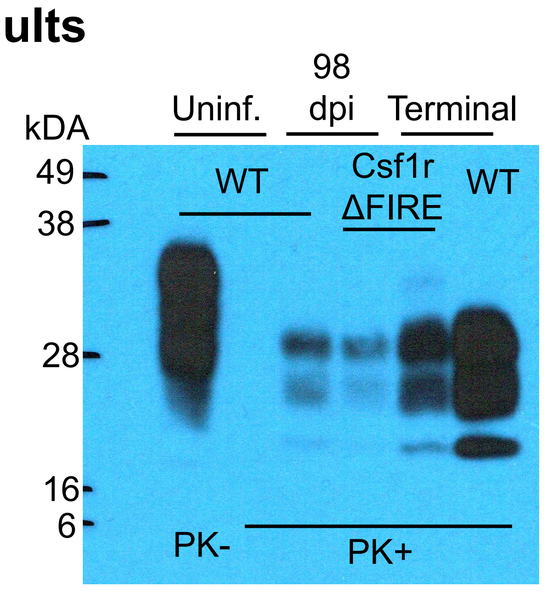
Microglia-deficient Csf1rΔFIRE mice and WT littermates were infected intracerebrally with prions. A group of prion-infected mice were sacrificed 98 days post infection and the remaining mice were observed for clinical signs of prion disease. Brains were analysed by RT-qPCR, Western blot and immunohistochemistry.

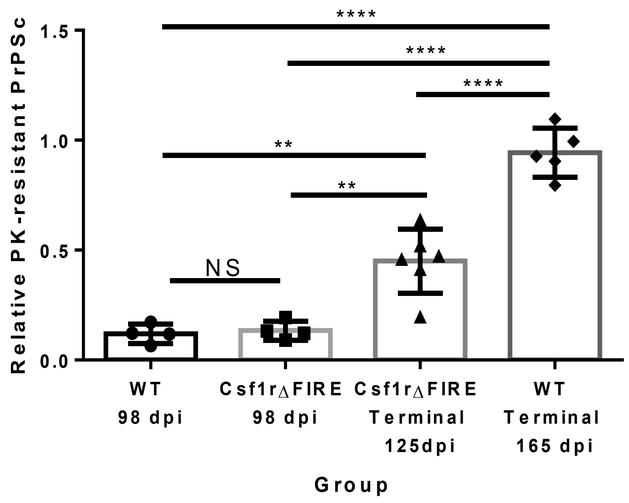
Results



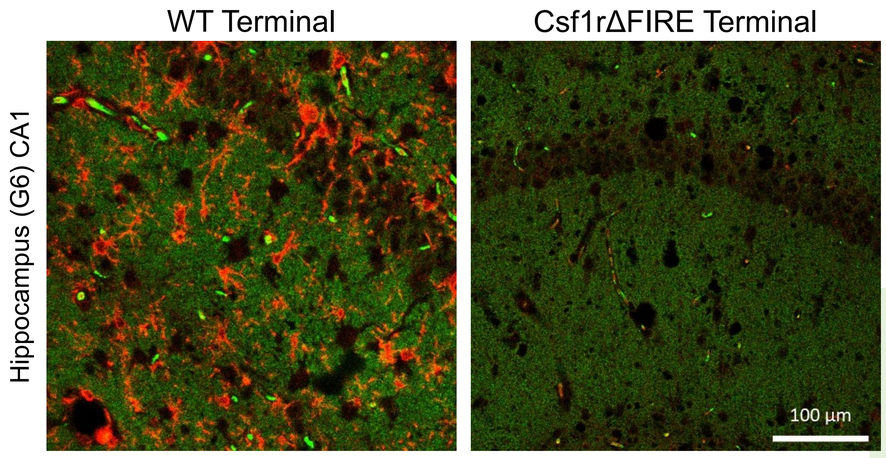


Prion disease pathogenesis is accelerated in Csf1rΔFIRE microglia-deficient mice.
Csf1rΔFIRE mice infected with prions had a significantly shorter disease incubation period than WT littermates, displaying clinical signs of prion disease at 100 days post infection. Prion-specific vacuolation at 98 dpi was more severe in Csf1rΔFIRE mice, however at the terminal stage of prion infection vacuolation was of similar severity to WT despite the shorter disease incubation period.

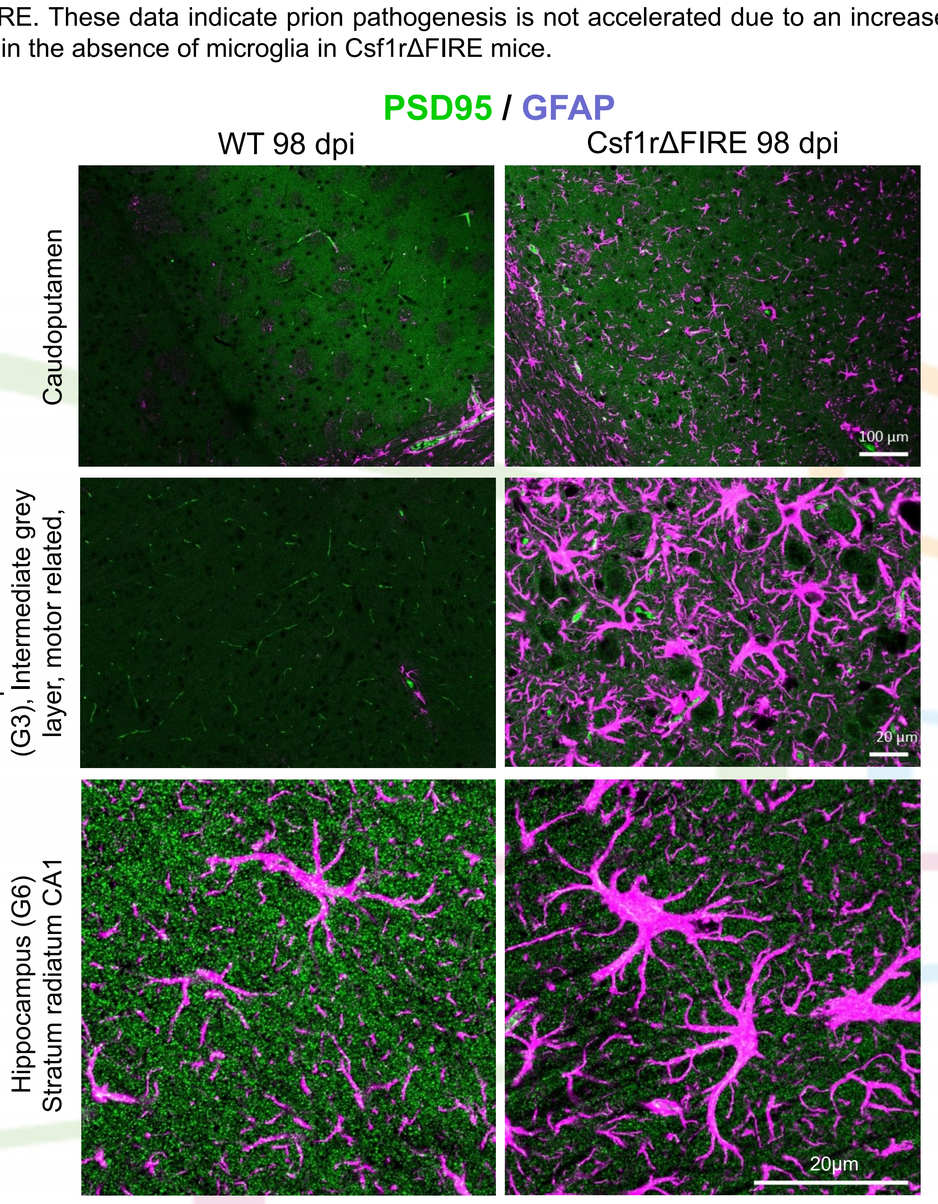




Microglia do not play a role in the degradation and clearance of prions.
Previous studies have suggested microglia function to uptake and degrade prions, thereby limiting infection. To visualise prion accumulation, brain protein homogenates were subjected to proteinase K (PK) digestion before Western blotting and immunodetection with anti-prion protein antibody BH1. We observed Proteinase K resistant prions accumulated in the brain at the same rate in both WT and Csf1rΔFIRE. These data indicate prion pathogenesis is not accelerated due to an increased build-up of prions in the absence of microglia in Csf1rΔFIRE mice.



The extensive microglial response following prion infection in WT mice is completely absent in Csf1rΔFIRE mice.
Csf1rΔFIRE mice revealed no evidence of microglia or invading monocytes throughout prion infection. Prion infected Csf1rΔFIRE mice also exhibited no detectable gene expression of microglial markers.



Astrocytosis activation and synaptic uptake is increased in Csf1rΔFIRE mice 98 days post prion infection.
Csf1rΔFIRE mice infected with prions exhibited earlier astrocyte activation in numerous brain regions concurrent with increased prion vacuolation. Synaptic loss and engulfment was visualised via uptake of post-synaptic density protein 95 (PSD95) uptake, in Csf1rΔFIRE mice synaptic loss is mediated solely via astrocytes.

Conclusions

Microglial-deficient Csf1r-FIRE mice are a useful model for studying homeostatic and neurodegenerative roles for microglia.
Prion infection is accelerated in the absence of microglia.
Microglia do not play a role in the clearance and degradation of prions but inhibit astrocyte activation and synaptic loss.
These results suggest the major role of microglia is the maintenance of homeostatic states in other CNS cell types

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